Brief Report

Cholesterol atheromatous embolism: an increasingly recognized cause of acute renal failure

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Abstract

Background. Cholesterol atheromatous embolism is a systemic disease resulting from cholesterol crystal embolization to many organs, including the kidney. Vascular surgery, vascular radiology investigations and anticoagulation have been identified as inciting factors.

Methods. Fifteen patients with extensive atherosclerosis, presenting with simultaneous occurrence of acute renal failure and peripheral ischaemic changes were diagnosed as having acute renal failure due to cholesterol atheromatous embolism.

Results. The patients, 12 men and three women, had an average age of 65 years. In one patient, spontaneous occurrence of the disease was observed. An inciting factor was identified in 14 patients: aortography in 10, aortic surgery in two, and thrombolysis in two. Clinical course of acute renal failure was quite variable. Four patients required dialysis; 11 were conservatively managed. All patients had concomitant skin lesions, including digital mottling, cyanosis and gangrene of the toes, and livedo reticularis of the lower limb and abdomen. Eosinophilia was the most common laboratory abnormality. The diagnosis of cholesterol atheromatous embolism was confirmed by tissue examination in eight; in three it was based on the finding of retinal cholesterol emboli; in four patients it was made on clinical grounds. Seven patients died within 36 months. Death was most commonly from cardiac causes.

Conclusions. Since the population at risk for cholesterol embolism is growing and the disease is iatrogenic in origin, we should expect to detect cholesterol embolism with greater frequency as cause of acute renal failure in the future.

Key words: acute renal failure; cholesterol embolism

Introduction

Cholesterol atheromatous embolism is a multisystem disease resulting from cholesterol crystal embolization to many organs, including the kidney, skin, brain, eye, gastrointestinal tract and extremities [1–5]. As a pathological entity, it first was described by Flory five decades ago [6]. However, recognition of its importance as a clinical entity has been slow. Antemortem clinical diagnosis of the disorder may be difficult, because it may present with non-specific manifestations that mimic other systemic diseases, particularly vasculitis [7]. The diagnosis of renal cholesterol atheromatous embolism should be suspected when renal failure develops shortly after aortic manipulation or in association with anticoagulant therapy, particularly if there are signs of extrarenal cholesterol emboli, such as gangrenous lesions in the toes and livedo reticularis in the lower body [1–5]. Other potential manifestations of cholesterol embolism include visual deficits or orange plaques in the retinal arterioles and abdominal pain due to pancreatic or mesenteric ischaemia [8,9]. Recently, eosinophilia and hypocomplementaemia have been found during the active phase of the disease [10,11]. In this report we describe 15 cases of acute renal failure occurring in the setting of cholesterol atheromatous embolism, which we have observed in our Institution in the last 6 years.

Subjects and methods

Between June 1989 and June 1995, 15 patients (12 men and 3 women) meeting the following criteria were identified at our Institution: (1) acute renal failure occurring in elderly subjects with extensive atherosclerotic vascular disease (2) simultaneous occurrence of ischaemic changes to the lower abdomen and extremities, including livedo reticularis, mottling, cyanosis or gangrene of the toes. These 15 patients were diagnosed as having acute renal failure due to cholesterol atheromatous embolism. The diagnosis was confirmed by tissue examination in eight and by cholesterol retinal deposits in three cases; it was made on clinical grounds in four cases.

Results

Between June 1989 and June 1995, 198 patients with acute renal failure were investigated at Department of
## Table 1. Clinical and laboratory findings of the 15 patients with renal CAE

| Pt. No. | Age years | Sex | Prior medical problems | Presenting symptoms and signs | Inciting event; interval to onset of renal CAE | S. creatinine (mg/dl): basal value/at diagnosis/at last follow-up | Eosinophils % and total count | Retinal deposits | Histologic diagnosis | Outcome (Follow-up) |
|---------|-----------|-----|------------------------|-------------------------------|-----------------------------------------------|----------------------------------------------------------------|--------------------------------|-------------------|-------------------|-------------------|---------------------|
| 1       | 56        | M   | Hypertension, coronary artery disease, diabetes, peripheral vascular disease | ARF, hypertension cyanosis and gangrene of the toes | Coronary angiography 6 days | 1.1/4.0/14.0 | 8%; 800 | No | Renal biopsy | HD (52) |
| 2       | 69        | M   | Hypertension, diabetes, CRF cerebrovascular disease peripheral vascular disease | ARF, hypertension livedo reticularis cyanosis of the toes, cerebral involvement weight loss | n.d. | 2.0/9.5/12.0 | n.d./n.d. | No | Renal biopsy | HD cardiac death (6) |
| 3       | 57        | M   | Hypertension, coronary artery disease | ARF, hypertension livedo reticularis cyanosis of the toes | Thrombolytic therapy; 21 days | 1.4/7.0/5.0 | 8%; 912 | Yes | n.d. | CRF cardiac death (18) |
| 4       | 60        | M   | Hypertension, diabetes CRF, cerebrovascular disease peripheral vascular disease | ARF hypertension cyanosis of the toes | Aortography 7 days | 1.9/5.5/5.0 | 8%; 1064 | Yes | n.d. | CRF cardiac death (2) |
| 5       | 75        | M   | Hypertension, CRF cerebrovascular disease peripheral vascular disease | ARF, hypertension cyanosis and gangrene of the toes, cerebral involvement | Aortography; 15 days | 3/10.0/12.0 | 5%; 300 | Yes | n.d. | CAPD cerebral death (36) |
| 6       | 64        | M   | Hypertension, coronary artery disease, CRF cerebrovascular disease peripheral vascular disease | ARF, hypertension, livedo reticularis, gangrene of the toes, weight loss | Aortography; 25 days | 2.6/8.5/4.5 | 1%; 99 | No | n.d. | CRF (36) |
| 7       | 66        | M   | Hypertension, coronary artery disease, peripheral vascular disease | ARF, hypertension cyanosis of the toes | Coronary angiography 20 days | 1.4/18.0/15.0 | 20%; 2260 | No | Autopsy | HD cardiac death (1) |
| 8       | 61        | M   | Hypertension, peripheral vascular disease coronary artery disease, aortic aneurysm | ARF, hypertension, livedo reticularis, cyanosis and necrosis of the toes | Aneurysm resection and graft 7 days | 1.3/7.3/6.5 | 2%; 200 | No | Skin biopsy | CRF (34) |
| 9       | 68        | M   | No underlying disease | ARF, hypertension, cyanosis of the toes | Thrombolytic therapy; 3 days | 1.1/5.3/4.5 | 10%; 560 | No | Skin biopsy | CRF (30) |
| 10      | 68        | M   | Coronary artery disease | ARF, hypertension, ischaemic colitis, livedo reticularis, gangrene of the toes, weight loss | Coronary angiography 20 days | 1.2/9/10.0 | 7%; 633 | No | n.d. | CAPD; death from ischaemic colitis (14) |
| 11      | 67        | F   | Hypertension, aortic aneurysm | ARF, hypertension, livedo reticularis, cyanosis and gangrene of the toes | Aneurysm resection and graft 3 days | 0.8/6.7/3.0 | n.d.; n.d. | No | n.d. | CRF (15) |
Renal cholesterol atheromatous embolism

Nephrology of University of Brescia, a renal unit which serves a population of 600 000 inhabitants. In 15 patients (7%), diagnosis of acute renal failure secondary to cholesterol atheromatous embolism was made. The average age of the patients was 65, with a range from 56 to 75 years. The main clinical features and laboratory findings of the patients are summarized in Table 1. At the time of diagnosis, all patients but one had a prior history of arterial hypertension, coronary artery disease, peripheral vascular disease, cerebrovascular disease, renal failure or diabetes mellitus. Sonography revealed irregular atherosclerotic plaques in suprarenal aorta in all patients. In seven patients, the degenerative vascular changes were confirmed by aortography. Three patients had an associated aortic aneurysm. Four patients had a unilateral renal artery stenosis, and one patient had a bilateral renal artery stenosis. A spontaneous occurrence of cholesterol atheromatous embolism was observed in only one patient. In 14 patients, a predisposing event was present: coronary or aortic angiography, via the femoral artery, in 10; aortic surgery in two; thrombolytic therapy for acute myocardial infarction (in the absence of any invasive causal procedure) in two patients. The interval from the inciting event to the onset of renal symptoms of cholesterol atheromatous embolism varied greatly. Acute renal failure developed 3–7 days after the invasive procedure in eight patients; in six patients it occurred after a longer time period (15–30 days). Acute renal failure was superimposed on various degrees of chronic renal failure in five patients. The clinical course of renal cholesterol atheromatous embolism was also quite variable and a spectrum of severity of renal impairment was observed. Acute renal failure required dialysis within a few days in four patients: two were treated by haemodialysis and two by peritoneal dialysis. After 1 year, the two patients on peritoneal dialysis regained sufficient renal function to stop dialysis. However, conservative management was associated with a difficult control of blood pressure and volume overload. Thus, the peritoneal dialysis was restarted in both patients after 2 and 3 months. A limited decline in renal function was managed conservatively in 11 patients; in 10 of them renal function slowly improved and stabilized; in one patient renal function continued slowly to deteriorate and haemodialysis was started within 48 months. Cutaneous manifestations of cholesterol atheromatous embolism occurred in all patients. They included digital mottling, cyanosis and gangrene of the toes, livedo reticularis of the lower limb and abdomen. Pedal pulses were most often normal. Usually, cutaneous lesions came before the onset of renal symptoms. Arterial hypertension was a common finding in our patients with cholesterol atheromatous embolism. A history of antecedent hypertension, exacerbated by the embolic disease, was present in 12 patients; in three patients, hypertension appeared de novo. A significant weight loss was observed in three patients, raising the clinical suspicion of systemic vasculitis. Cerebral involvement, including transient ischaemic attacks, changes in the level of
consciousness and gradual deterioration of neurological function was found in two patients. Retinal emboli were seen in three patients. Ischaemic colitis was the most important presenting symptom in one patient, in which a diagnosis of ulcerative colitis was considered. The most common laboratory abnormality was eosinophilia, defined as greater than 500 eosinophils/ml of blood. Thirteen patients had a well-documented full blood count performed of whom 10 had eosinophilia. In 12 patients serum complement was measured and discovered to be normal. The search for autoantibodies to neutrophil cytoplasmic antigens (ANCA) was negative in all patients. Urinalysis was remarkable for mild to moderate proteinuria and lacking active cellular casts, haematuria and leukocyturia. Histological confirmation of the diagnosis of cholesterol atheromatous embolism was obtained in eight patients. Two patients underwent a renal biopsy, which showed the widespread presence of needle-shaped cholesterol crystals in the lumina of medium-sized arterioles, sometimes surrounded by foreign-body giant cells. In addition to cholesterol emboli, ischaemic glomerular changes, varying degrees of sclerosis and arteriosclerotic changes and hyalinosis were commonly seen (Figure 1). In one patient, renal cholesterol atheromatous embolism was associated with classical lesions of diabetic nephropathy. Five patients had skin biopsy of the involved areas, demonstrating cholesterol clefts in the dermal vasculature (Figure 2). Autopsy was the means for histological diagnosis in one patient: cholesterol clefts were found in the arterioles of both kidneys. In three patients, the diagnosis was based on the presence of retinal cholesterol emboli. In the four remaining patients, the diagnosis of cholesterol atheromatous embolism was made on clinical grounds.

The outcome of our patients is summarized in Table 1. Seven of the 15 patients died: four within 12

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**Fig. 1.** Kidney biopsy (patient no. 1): Cholesterol clefts in a medium-sized artery, surrounded by multinucleated giant cells (H & E x 10).

**Fig. 2.** Skin biopsy (patient no. 15): small artery in the dermis containing cholesterol clefts, surrounded by multinucleated giant cells (H & E x 10).
months of diagnosis of cholesterol atheromatous embolism; three after 14, 18 and 36 months respectively. The cause of death was most commonly cardiac.

Discussion

Cholesterol atheromatous embolism is frequently overlooked as a cause of renal dysfunction during life [1–5]. However, it is reasonable to expect that, in the next few years, cholesterol embolization will be met with greater frequency as cause of acute renal failure. Several data support this view. First, the population at risk for this multisystem disease is enlarged by the increasing number of elderly subjects with aortic atherosclerosis. Second, the angiographic or vascular surgical procedures known to induce the syndrome are now accepted as routine practices in many hospitals. Third, the traditional inciting role of anticoagulation has been recently strengthened by the widespread use of thrombolytic therapy for acute myocardial infarction. In addition, anticoagulation is itself in more widespread use because of the evidence for its value in atrial fibrillation.

The retrospective analysis of our experience seems to agree with the above mentioned suggestions. We report here 15 cases of acute renal failure in the setting of cholesterol atheromatous embolism diagnosed at our Institution in the last 6 years. Before this period, this clinical entity was a rare event in our clinical practice. The increase of iatrogenic procedures performed at our hospital may probably account for increasing frequency of this diagnosis. During the 6-year period of our study, a total of 16 223 vascular procedures were performed in our Institution (12 973 coronary angiography; 3250 aortic angiography); in addition, 1020 patients underwent thrombolytic therapy for acute myocardial infarction.

Our data confirm that cholesterol atheromatous embolism occurs primarily in elderly patients who have extensive atherosclerosis. With the exception of one, our patients presented a well-known precipitating factor. Angiography, via the femoral artery, was the most frequent causal procedure. In two patients, cholesterol atheromatous embolism followed thrombolytic therapy: this is no surprise, since the effect of thrombolytic therapy is to lyse thrombi, including those covering atherosclerotic plaques [12, 13]. However, this complication is usually ignored in the mega-trials of the two methods.

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The biopsy of an involved tissue may be required to establish the diagnosis in patients with spontaneous disease or atypical clinical findings. Kidney is considered to be a common site for obtaining a diagnostic biopsy [1–5]. Skin biopsies have been suggested as an alternative when cutaneous lesions are present [17]. Another potential manifestation of systemic embolization, favoring the diagnosis, includes orange plaques in the retinal arteries. [1–5, 8].

In our series, histological confirmation of the diagnosis was obtained in 50% of patients. For three patients, diagnosis was based on the finding of retinal cholesterol emboli. In the remaining four patients, diagnosis was made on clinical ground alone: the concomitant presence of acute renal failure and peripheral ischaemic changes, the temporal association with a well-known inciting factor and the lack of another unifying pathology made this diagnosis reliable.

In summary, the kidney is a frequent target organ for cholesterol embolism. Since the population at risk for cholesterol embolism is growing and the disease is increasingly iatrogenic in origin, nephrologists should expect that cholesterol embolism will be found with greater frequency as cause of acute renal failure in the future.

References


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